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CME

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STATE-OF-THE-ART PAPER

# Stress Myocardial Perfusion Imaging for Assessing Prognosis: An Update

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# Stress Myocardial Perfusion Imaging for Assessing Prognosis: An Update

A strength of nuclear myocardial perfusion imaging (MPI) is the wealth of prognostic data accumulated over 30 years of experience with this technique. Nuclear MPI can predict outcomes and guide revascularization decisions in symptomatic patients and is well validated in special populations such as patients with diabetes and chronic renal disease. Known limitations, such as underestimation of ischemia and radiation burden, are being progressively reduced through advances such as positron emission tomography absolute flow quantification and fusion with computed tomography, new camera hardware and software, and stress-only protocols. Advanced statistical techniques and increasing focus on comparative effectiveness and appropriateness will continue to optimize nuclear cardiology going forward. (J Am Coll Cardiol Img 2011; 4:1305–19) 

Prognosis is primarily related to the degree of left ventricular dysfunction and the extent and magnitude of inducible myocardial ischemia. Radionuclide variables significantly supplement clinical and electrocardiogram (ECG) stress test variables in separating high- and low-risk subsets with respect to future hard cardiac events. Both hard (cardiac death or nonfatal myocardial infarction [MI]) and soft (e.g., revascularization or cardiac hospitalization) endpoints are often reported in combination. Readers of the literature should be aware that the annual event rates will vary depending on whether only hard endpoints, or the combination of hard and soft endpoints, are used. A recent occurrence in studies reporting the prognostic value of radionuclide imaging variables is the use of all-cause mortality as an endpoint. Caution should be exercised when using all-cause mortality in low- and intermediate-risk populations because most deaths in these population are noncardiac (1).

Over the past 30 years, many studies have been published supporting the prognostic value of stress myocardial perfusion imaging (MPI) in predominantly symptomatic patients (2). Initial clinical studies were undertaken with planar thallium-201 ($^{201}$Tl) imaging. They showed that the number of reversible defects and the presence of abnormal lung Tl-201 uptake were the most important variables in identifying high-risk patients with multivessel disease who had an increased risk of cardiac death or nonfatal MI. Those patients with normal findings on perfusion scans had a combined subsequent death or nonfatal infarction rate of <1% per year. Transient ischemic left ventricular (LV) cavity dilation was another high-risk variable that was associated with an adverse outcome. Transient ischemic dilation (TID) in most patients is due to extensive subendocardial ischemia post-stress that resolves on the resting scan. Later, single-photon emission computed tomography (SPECT) imaging supplanted the planar imaging technique for stress MPI, and the technetium-99m ($^{99m}$Tc)–labeled perfusion agents sestamibi and tetrofosmin, replaced Tl-201 as tracers for imaging. The transformation to SPECT with these imaging agents permitted gating of images and calculation of left ventricular ejection fraction (LVEF) and end-systolic and end-diastolic volumes and quantitation of regional wall motion or thickening abnormality extent. These functional variables provided additional prognostic information to perfusion variables (3).

Semiquantitation of perfusion abnormalities using indices such as the summed stress score (SSS) and summed difference score emerged as a more objective combined expression of the extent and severity of hypoperfusion or reversibility. These variables were derived from the accepted 17-segment model for SPECT. The percentage of LV ischemia and total ischemic total perfusion deficit were other perfusion variables demonstrated to separate patient subgroups. Those with >10% to 12% LV ischemia seemed to have a better outcome with revascularization than medical therapy (4). Vasodilator and dobutamine pharmacological stressors for MPI in patients unable to adequately exercise provided prognostic information similar to that with exercise stress MPI (5). However, the cardiac event rates with either normal or abnormal findings on pharmacological stress SPECT scans were higher than seen with post-exercise stress. This was attributed to the fact that patients referred

for pharmacological stress were a clinically higher risk population (e.g., older, more peripheral vascular disease, more chronic pulmonary disease, previous stroke).

In recent years, positron emission tomography (PET) MPI has been well validated as an alternative to SPECT for the detection of coronary artery disease (CAD) and determining prognosis. PET has certain advantages over SPECT, as discussed later in this review. It clearly can separate high- and low-risk patients based on extent of inducible perfusion abnormalities and/or the percentage of LV ischemia. Gated PET provides the same functional information as derived from gated SPECT, although LVEF can be derived at peak stress and rest rather than just 15 min to 1 h post-stress, as accomplished with gated SPECT studies. As discussed, quantification of absolute flow in milliliters/grams/minute and coronary flow reserve with PET allows even better risk assessment with MPI than just evaluating relative tracer uptake for defect detection.

The purpose of this review is to highlight some newer aspects of MPI for assessing prognosis, particularly in light of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial results, and the application of stress MPI in special populations such as patients with diabetes, patients with chronic kidney disease, and patients who have undergone an anatomic-based noninvasive test such as coronary computed tomography angiography (CTA) that is nondiagnostic or equivocal. Stress-only MPI may be considered for low-risk patients, which reduces radiation burden.

## RISK ASSESSMENT USING SPECT MPI

**Strength of evidence.** With respect to the American Heart Association/American College of Cardiology Practice Guidelines on Radionuclide Imaging, <5% of recommendations are identified as having level of evidence categorized as A (6). This is because there are few randomized studies comparing outcomes based on nuclear cardiology variables with other strategies (e.g., exercise ECG testing alone). Most recently, the WOMEN (What is the Optimal Method for Ischemia Evaluation in WomeN?) study randomized women with good functional capacity and a normal resting ECG to either exercise ECG testing alone or exercise ECG testing plus SPECT MPI. There were no differences in outcomes (7). This randomized trial should serve as a model for future SPECT MPI prognostic studies.

**Limitations of the current literature.** Some limitations to the prognostic studies published in the literature deserve mention. They include populations of patients that can be quite variable from study to study. Those studies that include older patients and a large percentage of patients with known disease and/or LV dysfunction have a high event rate with both normal and abnormal findings on MPI. Imaging methodology can differ markedly from study to study. Thus, using quantitative methods and attenuation correction may reduce the rate of false positives. When absolute flow and coronary flow reserve are assessed by quantitative PET, a higher percentage of multivessel disease will be detected with a corresponding lower prevalence of "normal" perfusion attributable to balanced ischemia.

**Implications of the COURAGE trial nuclear substudy.** In recent practice patterns, clinicians ordering stress MPI studies in patients with suspected or known CAD for the purposes of risk stratification would refer patients for invasive evaluation if the study findings were positive for inducible ischemia. Patients with normal findings on scans were most often treated medically or a workup for a noncardiac cause of symptoms was initiated. If a significant coronary stenosis was seen on angiography that correlated with the myocardial zone of hypoperfusion on SPECT, a percutaneous coronary intervention (PCI) such as stenting was performed.

This practice has been challenged after publication of the COURAGE Nuclear Substudy, which compared the effectiveness of PCI + optimal medical therapy (OMT) and OMT alone for ischemic reduction as assessed by SPECT MPI (8). Moderate to severe ischemia was defined as ≥10% LV ischemia. The primary endpoint was a ≥5% reduction in ischemic myocardium on a 6- to 18-month follow-up scan. At follow-up, the reduction in ischemic myocardium was greater when PCI was added to OMT than with OMT alone. More PCI + OMT patients demonstrated a significant ischemia reduction (33% vs. 19%; p = 0.0004), particularly in patients with moderate or severe baseline ischemia (78% vs. 52%; p = 0.007). This nonrandomized substudy

**ABBREVIATIONS AND ACRONYMS**

**CAD** = coronary artery disease
**CKD** = chronic kidney disease
**ECG** = electrocardiogram
**eGFR** = estimated glomerular filtration rate
**LV** = left ventricular
**LVEF** = left ventricular ejection fraction
**MACE** = major adverse cardiac event(s)
**MFR** = myocardial flow reserve
**MI** = myocardial infarction
**MPI** = myocardial perfusion imaging
**NRI** = net reclassification index
**OMT** = optimal medical therapy
**PCI** = percutaneous coronary intervention
**PET** = positron emission tomography
**SPECT** = single-photon emission computed tomography
**SSS** = summed stress score
**$^{99m}$Tc** = technetium-99m
**TID** = transient ischemic dilation

included only 314 of the 2,287 COURAGE subjects and was underpowered to detect clinical events. Moreover, this subgroup was found to have a lower clinical risk than the overall study cohort. Accordingly, although substudy subjects with ischemia reduction had a lower unadjusted rate of death or nonfatal MI ($p = 0.037$), especially in those with moderate to severe baseline ischemia ($p = 0.001$), these differences were not significant when Cox risk adjustment was performed ($p = 0.26$ and $p = 0.08$, respectively) (Fig. 1). However, patients with no residual ischemia with treatment had no cardiac events. It should be recalled that the main results of the COURAGE trial showed no difference in long-term outcome for stable patients with CAD randomized to an initial PCI strategy + OMT versus OMT alone. The COURAGE Nuclear Substudy suggests that PCI + OMT reduces ischemia to a greater degree than OMT alone in patients with moderate to severe ischemia, which may be associated with a better long-term prognosis, but additional study is required. Thus, the COURAGE Nuclear Substudy should be considered as hypothesis generating rather than definitive.

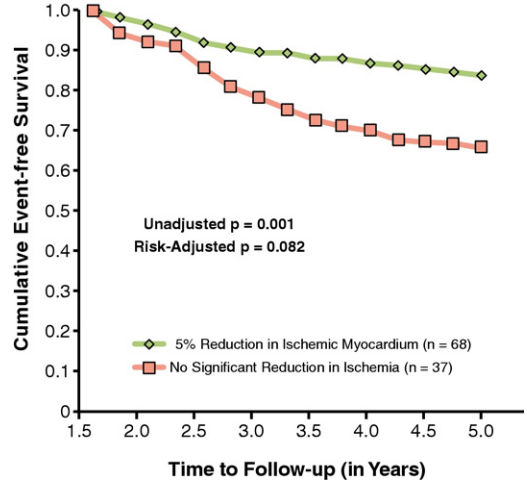


**Figure 1. Survival in the COURAGE Study Stratified by Presence or Absence of an Ischemia Reduction**

Kaplan-Meier survival analysis of the 105 patients in the COURAGE nuclear substudy with moderate to severe pre-treatment ischemia stratified by the presence or absence of a 5% reduction in myocardial ischemia after 6 to 18 months of optimal medical therapy or percutaneous coronary intervention plus optimal medical therapy. Overall event-free survival was 83.8% versus 66.0% for patients with and without a significant ischemia reduction ($p = 0.001$). In a risk-adjusted Cox model, this difference was not significant ($p = 0.082$). Adapted, with permission, from Shaw et al. (8).

The findings of this substudy formed the hypothesis for the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial. Until the results of this trial are known, practice has already changed in that patients with mild ischemia are now often not immediately referred for coronary angiography with a view to performing PCI for a significant stenosis. OMT is the first line of therapy. However, when ischemia is extensive, occurs at a low exercise workload, and/or is associated with significant functional abnormalities such as a depressed post-stress ejection fraction, an initial invasive strategy is certainly acceptable. The role of follow-up imaging to evaluate reduction or elimination of the ischemic burden is still unclear in asymptomatic patients after therapy is maximized. Serial imaging certainly increases the costs of medical services and exposes patients to more radiation. Nevertheless, if medical therapy is instituted for ischemia reduction and symptoms persist or increase, a crossover to an invasive strategy is warranted. Finally, it should be pointed out that in the overall COURAGE trial, patients with severe CAD (e.g., left main CAD) or high-risk ischemia were not randomized.

**Stress-only MPI for risk assessment.** The conventional 1-day SPECT imaging protocol most often entails performing a resting SPECT study first, followed by a stress study using higher doses of the tracer. This often involves a patient spending 3 to 4 h in the laboratory for 2 imaging acquisitions and is associated with substantial radiation exposure. Several investigators recently reported the prognosis of patients who had a stress-only study, the findings of which were normal after which the resting study was canceled. This approach is most applicable in patients with a low- or low-intermediate pre-test likelihood of CAD as the cause of presenting symptoms. Chang et al. (9) sought to determine whether normal findings on a stress-only SPECT MPI study conferred the same prognosis as normal findings on SPECT derived from stress and rest images. They reported all-cause mortality in 16,854 consecutive patients with normal findings on gated stress SPECT. Median follow-up was 4.5 years. Approximately one half of the patients underwent stress-only SPECT. At follow-up, no significant differences in patient mortality were seen between the 2 imaging protocols, although the stress-only subset received a 61% lower radiopharmaceutical dose. Figure 2 shows survival of stress-only and stress and rest SPECT subgroups with male and female patients analyzed separately (9). In this

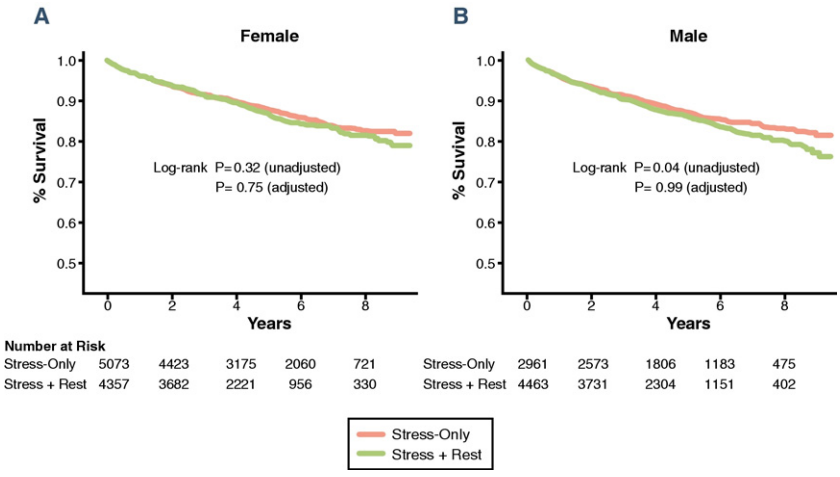


**Figure 2. Kaplan-Meier All-Cause Mortality Curves for Male and Female Patients Stratified by Receipt of a Stress-Only or Stress-Rest Protocol**

There was no difference in outcome in both male (p = 0.99) and female (p = 0.75) patients in a risk-adjusted Cox model. Adapted, with permission, from Chang et al. (9).

study, patients with diabetes with normal findings on stress-only SPECT had an outcome comparable to that of patients with diabetes with normal findings on stress + rest SPECT.

Duvall et al. (10) examined all-cause and cardiac mortality in 10,609 patients undergoing stress MPI, of whom 1,673 had normal findings on stress-only SPECT. Approximately 80% of these patients undergoing stress-only imaging had low pre-test risk, and 70% were outpatients. At the end of 40 ± 9 months of follow-up, the cardiac mortality was 0.4% in the group with normal findings on stress-only SPECT and 0.5% in the rest-stress cohort. No significant difference between the stress-only and rest-stress groups was found after controlling for confounding variables for both all-cause mortality (p = 0.94) and cardiac mortality (p = 0.82). It was estimated that the total radioisotope dose in the stress-only patients was reduced by 25%.

A stress-only strategy implies that the perfusion scan findings are normal and that attenuation artifacts can be distinguished from true perfusion defects. Stress-only imaging does not allow us to compute the TID ratio. However, TID in the presence of a normal gated SPECT study, observed in a patient with a low pre-test probability of CAD who can exercise to an adequate heart rate and/or workload, is usually artifactual (11). Thus, stress imaging should probably be done first in clinically lower risk patients like those who are seen in the emergency department of hospitals with atypical symptoms, a normal resting ECG, and no elevation of troponin. If the stress SPECT shows normal perfusion and function, the resting study can be cancelled. This approach will increase throughput in nuclear cardiology laboratories, reduce costs, and decrease radiation exposure to patients by as much as 25% to 60% (9,12).

**Underestimation of the extent of CAD with SPECT MPI.** It has been well recognized that stress SPECT MPI with either $^{99m}$Tc sestamibi or $^{99m}$Tc tetrofosmin underestimates the extent of CAD compared with coronary angiographic findings, particularly with vasodilator imaging (13). In the study by Lima et al. (14), only 25% of patients with angiographic 3-vessel CAD had perfusion defects or regional dysfunction in the supply regions of the 3 stenosed coronary arteries (Fig. 3). In fact, 12% had completely normal findings on SPECT MPI studies. Berman et al. (15) found that among 101 patients with ≥50% stenosis of the left main coronary artery and no previous MI or coronary revascularization, approximately 40% had a low-risk scan findings with <10% LV ischemia. This underestimation of CAD may be related to the low myocardial extraction relative to hyperemic flow changes of these $^{99m}$Tc MPI tracers and the fact that only relative perfusion is evaluated. If all 3 vessels are significantly narrowed or there is a combination of left main and multivessel CAD, uniform tracer uptake due to "balanced" ischemia may lead to rather homogeneous tracer uptake. Even semiquantitation may not identify this balanced ischemia and diffuse abnormal flow reserve.

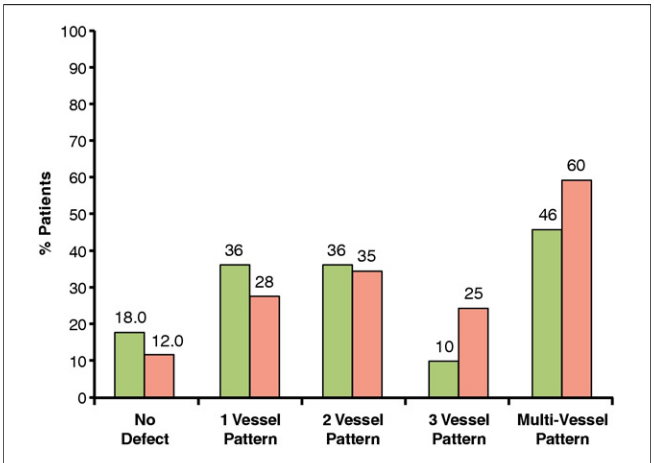


**Figure 3. SPECT Abnormalities by CAD Extent**

Prevalence of single-photon emission computed tomography (SPECT) perfusion or perfusion/function abnormalities by obstructive disease pattern on invasive coronary angiography. Patients with 3-vessel disease have a low (25%) prevalence of perfusion or functional defects, indicating the underestimation of multivessel disease by SPECT myocardial perfusion imaging. Reprinted, with permission, from Lima et al. (14). CAD = coronary artery disease.

The presence of extensive post-stress regional dysfunction and TID would suggest that the findings of the perfusion scan are not really normal, especially if the patient had inducible ischemic ST depression on the stress ECG or achieved a poor workload. This underestimation of CAD has prompted active investigation for quantitating flow reserve with PET technology (see section on PET imaging). Currently, research is being conducted in developing the technology for dynamic SPECT imaging for evaluating flow reserve (16).

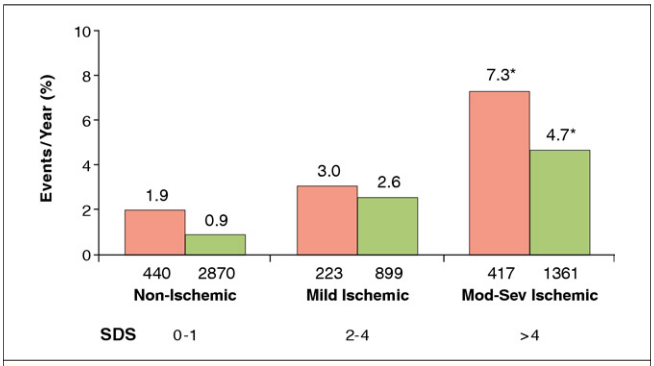


**Figure 4. Annualized Cardiac Events Stratified by Ischemia Severity and Presence of Diabetes Mellitus**

Yearly cardiac death/nonfatal myocardial infarction rate stratified by the degree of ischemia (summed difference score [SDS]) in patients with **(pink bars)** and without **(green bars)** diabetes mellitus. Event rates increase as a function of ischemia ($p < 0.001$). Adapted, with permission, from Kang et al. (21). Mod-Sev = moderate to severe.

## SPECIAL POPULATIONS

**Risk assessment by MPI in diabetes mellitus.** Patients with diabetes mellitus are a special population on which there is a robust amount of prognostic literature. The prevalence of diabetes is increasing dramatically, with >17 million individuals affected in the United States and 12% expected to be diabetic by 2050 (17,18). Patients with CAD and DM have a 2 to 8 times higher annual death rate, and cardiac event rates are not decreasing over time for patients with diabetes as they are in those without diabetes (17,19–21).

Multiple studies showed that SPECT MPI has incremental prognostic value over clinical risk factors and stress ECG for the assessment of cardiac death and nonfatal MI (21–23). Kang et al. (21) showed the annual rate of cardiac death and nonfatal MI to increase from 1% to 2% in patients with normal findings on SPECT MPI to >7% in those with moderate to severe ischemia (summed difference score >4) in 1,271 patients with diabetes (Fig. 4) (21). Several clinical factors provide additional risk stratification, including the degree of metabolic dysfunction present, the ability to exercise, and the presence of symptoms. Patients requiring combined insulin and oral agents have a 15- to 21-fold higher risk of events than those on either type of therapy alone, and the risk of events is higher in those taking insulin versus oral agents alone (24,25). Likewise, the inability to exercise during stress testing increases the risk of annual cardiac death 6.8-fold (from 1.3% to 8.8%, $p = 0.001$) (26). The presence of dyspnea significantly increases the risk of events in those with diabetes, with a 3-fold higher rate of cardiac death and nonfatal MI than in asymptomatic patients (13.2% vs. 3.4%, $p < 0.009$) (22). Interestingly, in this study, the event rate with angina was not significantly higher than in patients without symptoms (5.6% vs. 3.4%, $p = 0.44$) (22).

The substantial event rate in asymptomatic patients in this study is not surprising given the high rates of ischemia in asymptomatic patients in the landmark DIAD (Detection of Ischemia in Asymptomatic Diabetics) study (27). A 5-year follow-up of the DIAD study found that SPECT MPI provides good risk stratification, with a 6-fold higher risk of cardiac death/nonfatal MI in patients with moderate to large defects versus no or small defects (2.4% vs. 0.4%, $p = 0.001$). However, it does not appear that this information leads to improved clinical care because there was no significant decrease in cardiac death/nonfatal MI in

asymptomatic diabetic individuals screened for ischemia versus routine clinical care (27). One possible explanation for a lack of screening benefit is the lower risk of this population given that patients with known CAD were excluded. It is also possible that increased use of evidence-based medical therapy in both the screened and unscreened groups minimized the differences between them. This illustration of the power of intensive medical therapy is consistent with similar effects in the COURAGE and BARI-2D studies (28,29).

Although there was no benefit with revascularization across the entire BARI-2D population, the patients requiring coronary artery bypass graft surgery had improved survival, and the substudy looking at events stratified by ischemia is pending (29). However, data from 2 large observational cohorts totaling 11,453 patients (2,206 of whom were diabetic) suggest that patients with significant myocardial ischemia on SPECT MPI have improved survival with revascularization versus medical therapy in both symptomatic and asymptomatic diabetic patients (4,30).

Despite the prognostic benefit of SPECT MPI, the rate of cardiac events is unacceptably high in diabetic patients with normal myocardial perfusion (Fig. 5) (23,31). Giri et al. (23) showed that diabetic men have a 13.8% risk of death or MI at 3 years. This high rate is likely secondary to both false-negative studies for significant CAD by SPECT MPI and to the increased prevalence of mild stenosis with a higher risk of plaque rupture. It indicates that noninvasive techniques should be improved to more accurately diagnose CAD, as with the increased use of PET MPI, and that more aggressive medical therapy should be pursued (32).

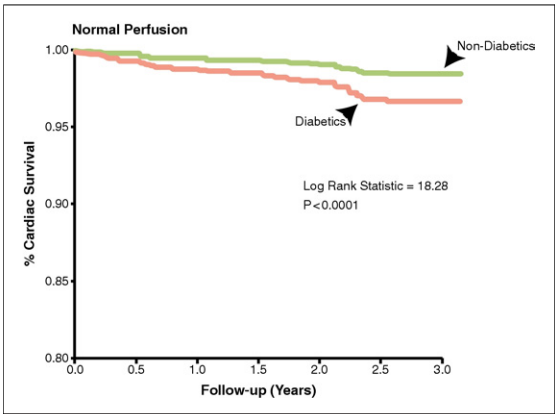


**Figure 5. Cardiac Event Rates in Diabetics and Nondiabetics With Normal Stress MPI**

Kaplan-Meier curves of survival free of cardiac death in diabetic and nondiabetic patients with normal stress myocardial perfusion imaging (MPI). Reprinted, with permission, from Giri et al. (23).

**Significance of SPECT MPI in patients with chronic renal disease.** In recent years, it has become quite apparent that patients with chronic kidney disease (CKD) are at high risk of future cardiac events. The risk of all-cause mortality, cardiac mortality, and prevalence of cardiovascular disease increases significantly in proportion to the decrease in renal function as measured by the estimated glomerular filtration rate (eGFR) (33,34). CKD patients have more than a 10- to 20-fold increased risk of cardiac death compared with age- and sex-matched subjects without CKD (35). Diabetic patients with CKD have a higher cardiac event rate than nondiabetic patients with CKD. Many patients with advanced CKD including those on dialysis may not manifest chest pain with severe CAD. Nephrologists who are considering patients for renal transplantation most often refer patients to either coronary angiography or noninvasive stress imaging for risk stratification and detection of CAD. Some CKD patients with known CAD may also be risk-stratified again when renal dysfunction becomes progressive.

Several studies have been published showing evidence of the value of stress SPECT MPI for prognostication in patients with CKD. In a predominantly male (97%) cohort with a high prevalence of diabetes (40%) and CAD (45%), Hakeem et al. (36) found a substantial increase in cardiac death once the eGFR decreased to $<60$ and the SSS exceeded 8.0. The annual rate of all-cause mortality and subsequent nonfatal MI was significantly higher in patients with an eGFR of $<60$ and perfusion defects compared with those with an eGFR of $>60$ with similar perfusion abnormalities. Patients with an eGFR of $\geq 60$ and normal findings on SPECT studies had an annual cardiac death rate of 0.8% versus 9.5% in those with defects demonstrated on SPECT and an eGFR of $<60$. In a subsequent publication by Hakeem et al. (37) in a cohort undergoing renal transplantation, the annual cardiac death rate was 16.8% for patients with CKD and diabetes who had an SSS $>8$. The highly selective nature of these studies may limit their generalizability. Al-Mallah et al. (38) also showed that the risk of all-cause mortality increased with worsening kidney function. Furthermore, at each stage of impaired renal function, patients with abnormal findings on SPECT MPI had an increased risk of adverse events. The magnitude of total perfusion defect and ischemia on MPI was

associated with worse outcome after adjusting for confounding variables including GFR and ejection fraction. Venkataraman et al. (39) showed that the larger the defect size was on vasodilator stress MPI, the worse the prognosis was for patients on long-term hemodialysis. Risk stratification was better achieved using defect size as the prognostic variable as opposed to the extent of angiographic CAD (Fig. 6). Interestingly, the event rate for patients with no significant stenosis was similar to the event rate for patients with 1- and 2-vessel disease.

Thus, these studies suggest that stress MPI can identify high-risk patients with CKD. Greater extents of inducible perfusion abnormalities and greater degrees of renal dysfunction are associated with higher risks of cardiac complications. What is yet to be ascertained is whether coronary revascularization improves outcomes in such patients with CKD and abnormal findings on SPECT MPI. No randomized studies have been performed comparing medical therapy with revascularization plus medical therapy in patients with advanced CKD and abnormal findings on MPI.

**MPI risk assessment in women and the elderly.** SPECT MPI is an especially important risk assessment tool in elderly patients. Many elderly patients have comorbidities or physical deconditioning that render them incapable of performing exercise stress. MPI in the elderly has been shown to be safe and effective, with a low rate of cardiac events after normal perfusion studies similar to that for younger patients (40). Hachamovitch et al. (41) showed an incremental value of ischemia over other clinical data in 5,200 patients 75 years of age and older. This proven benefit of MPI is especially important given the diminished role of coronary CTA in the elderly due to a higher prevalence of coronary artery calcification.

Women undergoing evaluation for ischemia are a large subgroup that has long been thought by many to require SPECT MPI imaging due to a higher false-positive rate on stress ECG alone. Observa-

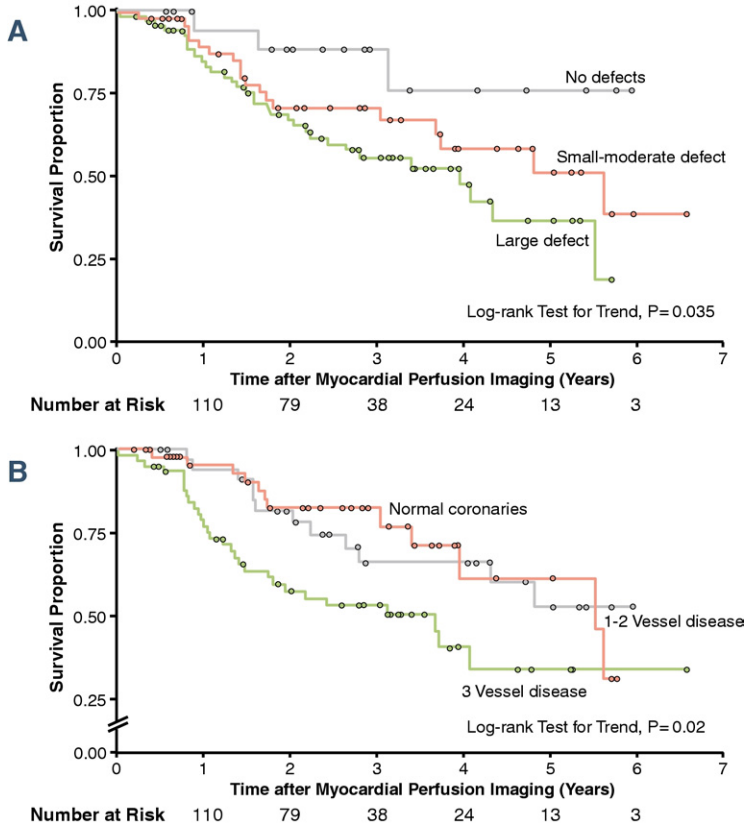


**Figure 6. Survival in End-Stage Renal Disease Stratified by Extent of CAD and SPECT Defect Size**

Kaplan-Meier survival curves for patients with end-stage renal disease stratified by single-photon emission computed tomography perfusion defect size **(A)** and extent of obstructive coronary artery disease on coronary angiography **(B)**. Adapted, with permission, from Venkataraman et al. (39). Abbreviations as in Figure 3.

tional cohorts (42,43), such as the 2,225-patient study by Cerci et al. (43), have shown an incremental prognostic benefit of SPECT MPI over other clinical variables and left ventricular function. However, the WOMEN study of 824 women randomized to exercise ECG versus exercise MPI found comparable major adverse cardiac event (MACE) rates in women with normal test results (0.4% for exercise ECG vs. 1.2% for exercise MPI) (44). These findings suggest that similar low-risk patients with good functional capacity and no known CAD should undergo exercise ECG as their initial test for ischemia.

## RISK ASSESSMENT BY CARDIAC PET MPI

**Myocardial ischemia evaluation by PET MPI.** PET MPI has many advantages over SPECT, including improved spatial and temporal resolution, intrinsic attenuation correction, and increased count sensitivity. These benefits lead to improved image quality, diagnostic accuracy, interpretive confidence, and detection of balanced ischemia (32,45).

Despite these advantages, PET MPI has historically been underused due to costly equipment, the need for a local cyclotron for tracer generation, a paucity of prognostic information, and the inability to use exercise as the mode of stress. The use of PET MPI is now increasing due to resolution of many of these limitations. Equipment costs are decreasing, rubidium-82 ($^{82}$Rb) can be generated without a cyclotron, and a novel [18]-fluorodeoxyglucose ($^{18}$F)–based tracer is under evaluation that will allow exercise stress testing (45,46).

As PET MPI has become more common, the prognostic literature has become more robust. PET perfusion abnormalities have been shown to provide incremental prognostic value by chi-square analysis in 4 major studies totaling 3,897 subjects (47–50). Marwick et al. (47) showed the presence and extent of ischemic myocardium to predict a composite of cardiac death, nonfatal MI, late revascularization, and unstable angina in 685 patients undergoing dipyridamole $^{82}$Rb PET MPI. Yoshinaga et al. (49) stratified 367 patients undergoing $^{82}$Rb PET by SSS and found a stepwise increase in the rates of cardiac death and nonfatal MI at a mean follow-up of 3.7 years as the SSS increased: 0.4% for an SSS $<4$; 2.3% for an SSS of 4 to 7; and 7.0% for an SSS $\geq 8$. It should be noted that 29 of the 46 events (63.0%) were revascularization procedures rather than hard cardiac events. An important novel finding of this study was that patients who were referred for PET MPI after $^{99m}$Tc-SPECT had a markedly different cardiac event rate with a normal versus abnormal PET SSS (1.3% and 15.2%, $p < 0.001$, respectively). However, it should be noted that 1 nonfatal MI was the only one of 11 events that was "hard."

A study by Dorbala et al. (50) included a much larger sample size of 1,432 patients who underwent vasodilator $^{82}$Rb PET MPI with fewer exclusions and contemporary imaging techniques. Over a mean follow-up of 1.7 years, the percentage of ischemic myocardium correlated closely with the risk of cardiac death or nonfatal MI. Patients without ischemia had a 0.7% annualized event rate, which increased to 11% for those with >20% LV ischemia (Fig. 7). The percentage of ischemic myocardium provided incremental prognostic value both for these cardiac events ($p = 0.04$) and for all-cause mortality ($p = 0.006$). A similar study of 1,441 patients by Lertsburapa et al. (48) showed the SSS by $^{82}$Rb PET MPI to predict all-cause mortality (2.4% for an SSS of 0 to 3; 4.1% for an SSS of 4 to 8; 6.9% for an SSS >8; $p < 0.001$). This study also showed the LVEF to provide incremental prognostic information as with SPECT.

However, in contrast to LVEF determination by SPECT, the gated $^{82}$Rb PET images are acquired at the time of stress rather than after a delay.

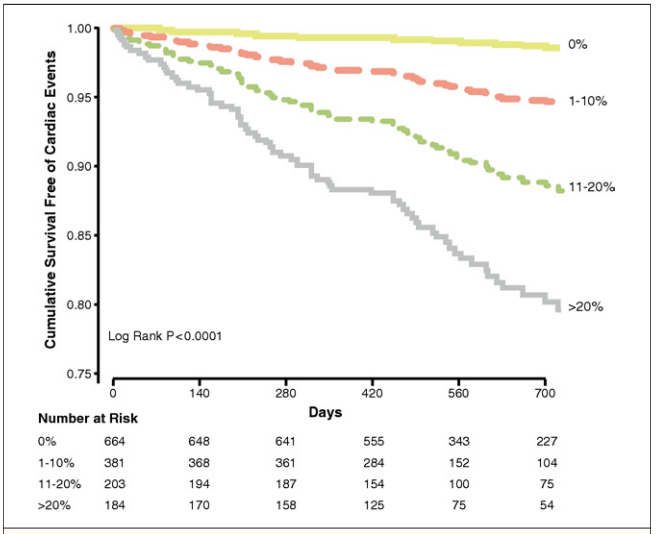


**Figure 7. Cardiac Events Stratified by Percentage of Ischemic Myocardium on Rb-82 PET MPI**

Kaplan-Meier curves of survival free of cardiac events as a function of the percentage of ischemic myocardium in patients undergoing rubidium-82 positron emission tomography (PET) myocardial perfusion imaging (MPI). Higher ischemic burden significantly increases the risk of cardiac events ($p < 0.0001$). Reprinted, with permission, from Dorbala et al. (50).

Accordingly, changes in LV function between rest and stress have increased diagnostic and prognostic significance. In 510- and 1,432-patient studies, Al-Mallah et al. (38) elegantly showed that the LVEF reserve (stress LVEF − rest LVEF) is a strong independent predictor of severe ischemia, left main/3-vessel CAD, and adverse events. Patients with left main/3-vessel CAD have a mean reserve of −6.7%. On the other hand, an LVEF reserve of +5% has a negative predictive value of 97% for excluding severe left main/3-vessel CAD. An LVEF reserve of <0 is associated with a >2-fold increase in cardiac events and all-cause mortality (Fig. 8). LVEF reserve provided incremental prognostic value over clinical variables and PET perfusion results (50). Therefore, a positive LVEF reserve in the setting of a normal perfusion result is reassuring, whereas a negative LVEF reserve may warrant further testing, even in the setting of normal perfusion. Further study of this phenomenon with adenosine stress (which may lead to less prolonged ischemia than dipyridamole due to its shorter half-life) is warranted (45).

Although there is a wealth of multicenter studies assessing prognosis with SPECT MPI, the current PET MPI prognostic literature is based on single-center retrospective analyses and could benefit from prospective multicenter validation studies (45). SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD) is a 41-center observational registry that will help better characterize the prognostic role of PET MPI and PET-CT (51).

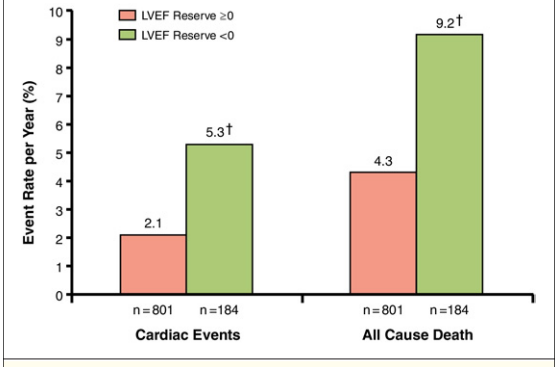


**Figure 8. Effect of LVEF Reserve on Cardiac Events and Mortality**

Rates of cardiac death/nonfatal myocardial infarction and all-cause mortality by left ventricular ejection fraction (LVEF) reserve in patients undergoing rubidium-82 positron emission tomography myocardial perfusion imaging. Event rates increase with LVEF reserve <0% ($p < 0.001$). Reprinted, with permission, from Dorbala et al. (50).

## ADVANCES IN SPECT AND PET MPI FOR PROGNOSTIC EVALUATION

**PET-CT fusion imaging.** There are several future advances expected in PET MPI that will likely transform the prognostic literature. Although there are few robust prognostic data available for PET-CT, this combined modality offers the potential to simultaneously assess the presence of obstructive CAD and evaluate its ischemic burden, thereby overcoming the limitations inherent in each technique alone (52). Calcium scoring adds incremental prognostic value to PET MPI. Nonetheless, 16% of patients with ischemia have a calcium score of 0, possibly due to obstructive soft plaque (53). For this reason, coronary CTA is the anatomic test of choice to assess the extent and severity of coronary atherosclerosis. However, coronary CTA is insufficient as a single test for the assessment of atherosclerotic disease because only 40% to 50% with ≥50% stenoses on coronary CTA have evidence of myocardial ischemia (54,55). Fusion of the PET and CT images also allows for culprit lesion determination. Technical advances have made this a more feasible option by significantly reducing the radiation burden to consistently <10 mSv (52). Advances in molecular imaging may soon allow the identification of vulnerable atherosclerotic plaques, which may allow improved risk stratification and selection of therapeutic goals (56).

An additional advantage of PET-CT angiography over PET alone is the prognostic value of nonobstructive CAD (57,58). In a meta-analysis of 9,592 patients, Hulten et al. (57) showed an incremental increase in MACE for nonobstructive CAD over no CAD (1.4% vs. 0.2%). The finding of nonobstructive CAD may trigger more aggressive risk factor modification, as shown in the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study of the effect of calcium scoring (59). A functional study alone does not provide this information. The optimal use of PET-CT has not been established. In this era of cost-containment for cardiovascular imaging, assessment of the cost-effectiveness of this technique and identification of the ideal clinical indications and patient populations will be essential. Improved diagnostic accuracy will not be enough. For widespread adoption of PET-CT to occur, it will need to reduce subsequent adverse cardiac outcomes over testing with either PET or coronary CTA alone. The SPARC observational registry should assist in this evaluation (51).

**Absolute flow quantification and myocardial flow reserve.** Absolute myocardial blood flow in millimeters/grams/minutes can be quantified using PET imaging. This technique allows the calculation of the myocardial flow reserve (MFR), which is the ratio of myocardial blood flow at peak hyperemia to resting myocardial blood flow. MFR has been shown to identify multivessel disease and predict the extent of ischemia more accurately than relative perfusion techniques (60,61). Equivocal studies from flow heterogeneity at higher flow rates are reduced as well (60). Prognostic data, although limited, are starting to emerge. Herzog et al. (62) assessed 229 patients who underwent 13N-ammonia PET perfusion imaging. An abnormal MFR <2.0 was found to be independently associated with the 3-year rate of both MACE (6.3% vs. 1.4%, $p < 0.05$) and cardiac death (3.1% vs. 0.5%, $p < 0.05$). MFR predicted an increased risk in patients with abnormal perfusion (Fig. 9).

The most commonly used PET perfusion tracer is $^{82}$Rb because of its availability without an on-site cyclotron. The decreased tracer uptake at higher coronary flow rates necessitates a corrective factor, but absolute flow estimates correlate well with 13N-ammonia–derived values (63). Limited prognostic data had been available for absolute flow quantification using this tracer. Fukushima et al. (64) retrospectively studied 224 patients undergoing $^{82}$Rb PET perfusion imaging and found that an MFR less than the median for this population (<2.11) was associated with a hazard ratio of 2.93 for cardiac events. However, 2 recent papers have strengthened the link of reduced MFR and adverse cardiac outcomes. Ziadi et al. (65) demonstrated that an MFR <2 was an independent predictor of hard events (hazard ratio: 3.3) and MACE (hazard ratio: 2.4). Murthy et al. (66) found a 5.6-fold increase in the risk of cardiac death for those with an MFR <1.5 and a correct reclassification of 34.8% of intermediate-risk patients.

Additional comparative effectiveness studies between absolute and relative flow techniques for the assessment of clinical outcomes, cost-effectiveness, and quality of life will be essential.

**New PET tracers.** Exercise capacity is one of the most powerful prognostic markers obtained during exercise stress testing (1,67). The inability to perform exercise stress testing has been a major limitation of $^{82}$Rb and $^{13}$N-ammonia PET MPI. A novel $^{18}$F tracer in clinical evaluation has >90% first-pass extraction and specific uptake across a wide range of flow rates (46). It has a high signal-to-noise ratio, and initial assessments of image

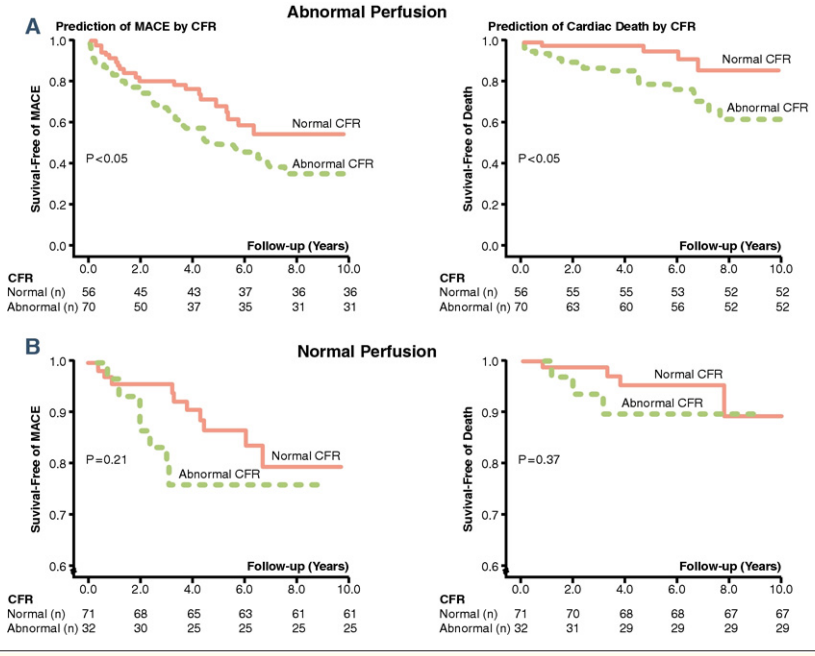


**Figure 9. Cardiac Events Stratified by Perfusion Abnormalities and Coronary Flow Reserve**

Unadjusted Kaplan-Meier curves for survival free of major adverse cardiac events and cardiac death stratified by normal coronary flow reserve (CFR) (>2.0) versus abnormal (<2.0) in patients with abnormal **(A)** and normal **(B)** perfusion. Abnormal CFR predicts events irrespective of perfusion findings. Reprinted, with permission, from Herzog et al. (62).

quality with this agent are very promising, having been judged superior to $^{13}$N-ammonia images in early animal studies (68). The long half-life (110 min) of $^{18}$F will allow exercise stress testing to be performed for PET MPI studies using this tracer. Its long half-life will also allow centers without on-site cyclotrons to engage in cardiac PET imaging without the expense and subsequent high patient throughput required for $^{82}$Rb generator use (69). Absolute flow quantification will likely be available with this tracer (70).

**Improved statistical evaluation.** Finally, more rigorous statistical evaluation of the prognostic benefit of SPECT and PET MPI should be undertaken. Contemporary statistical techniques, such as the net reclassification index (NRI), which assesses the ability of a test to reclassify patients into their proper risk categories, are now recommended (71). This method is robust and easier to apply clinically versus other existing techniques such as area-under-the-curve analysis. For example, Shaw et al. (72) used the NRI to determine that the additional cost of correctly classifying 1 additional person at high or low risk of cardiovascular death or nonfatal MI was $615 for stress MPI versus exercise stress ECG. Piccini et al. (73) identified an increased risk of sudden cardiac death in patients with CAD and an LVEF >35% and increasing SSS. However, the NRI showed that their SPECT-derived nomogram failed to reclassify 77 of 79 sudden cardiac deaths as high risk, providing an important clinical perspective. Although it has not been widely used in the SPECT prognostic literature, this statistical tool may assist in comparing the effectiveness and appropriateness of different imaging methods for prognostic assessment in ischemic heart disease (74).

## CONCLUSIONS

In summary, there is no doubt that variables derived from stress MPI provide clinically useful prognostic information in symptomatic patients with suspected or known CAD. For many years, we have primarily relied on exercise or pharmacological SPECT MPI for detecting CAD and risk stratification. Quantitative analysis of relative perfusion abnormalities (i.e., defect extent and magnitude relative to segment of maximal tracer uptake) and functional information derived from gated images have yielded more robust and accurate prognostic information. Patient selection for SPECT MPI has also been refined by introduction of appropriateness criteria and by greater consideration to radiation risk versus clinical benefit (75). The advent of stress-only imaging and emergence of new camera hardware and software programs have contributed to reducing radiation exposure from SPECT MPI. We have a better understanding of why some patients with multivessel CAD have uniform tracer uptake on MPI, which may reflect balanced ischemia and diffuse abnormal coronary flow reserve. Quantitative dynamic PET imaging permits the determination of absolute flow and coronary flow reserve, the ratio of peak stress flow to resting flow. Using PET MPI with flow quantitation can thus improve the detection of high-risk patients. Unfortunately, this approach is not available in most nuclear cardiology laboratories, but the advent of hybrid PET-CT cameras should lead to more widespread adoption of cardiac PET in major imaging centers. With SPECT, patients with diffuse ischemia can often be identified by nonperfusion variables such as TID and regional dysfunction on gated images. Certain populations, such as symptomatic patients with diabetes or CKD, benefit from noninvasive perfusion assessment to identify high-risk subsets of patients who have been shown to experience a high rate of cardiac events. We may see more MPI studies being performed in patients who have initially undergone coronary CTA for chest pain and are found to have intermediate lesions or extensive noninterpretable segments. MPI in these situations assess the physiologic significance of such anatomic abnormalities.

Finally, in this era of cost-containment with respect to the use of imaging tests, we need to decrease the use of inappropriate tests. Possible strategies include eliminating the use of MPI in asymptomatic subjects as the initial test for risk assessment or performing MPI studies in asymptomatic patients after uncomplicated revascularization. Undoubtedly, there will be further advances in technology, and it is incumbent on investigators in the imaging field to determine their worth versus less expensive technology. The application of NRI concepts to new imaging tests or indications is key to the understanding of the additional benefit of an imaging modality to other known variables.

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**Key Words:** coronary artery disease ■ myocardial perfusion imaging ■ prognosis.

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